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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/646,970	08/21/2003	Carol J. Phelps	10758.105009	3048

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EXAMINER	
SGAGIAS, MAGDALENE K	
ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/646,970	PHELPS, CAROL J.	
	Examiner	Art Unit	
	MAGDALENE K. SGAGIAS	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,43-46 and 48-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21,43-46 and 48-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 September 2004;8/21/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/3/09 has been entered.

Applicant's arguments filed 4/3/09 have been fully considered but they are not persuasive. The amendment has been entered. Claims 1-21, 43-46, 48-65 are pending and under consideration. Claims 22-42, 47 have been canceled.

Allowable Subject Matter

Claims **19-21 remain** objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims **1-8, 13, 17-18, 43, 48, 60, 62 remain** rejected under 35 U.S.C. 102(e) as being anticipated by **Hawley et al,** (US 2006/0242722 A1) for the reasons of record of the previous office action mailed 10/03/08.

Applicants argue that both conception and reduction to practice of the present invention was completed prior to Hawley's provisional filing date. Applicants direct the Examiner's attention to New Scientist, "Mini-Pig Clone Raises Transplant Hope", January 13, 2003, provided with the May 16, 2008 response in this case. In this article, it is noted that the pigs of the present invention were born in July, 2002, prior to both the birth of the pigs described in Hawley and, more importantly, prior to the Hawley priority application. Additional evidence showing that the present invention was completed prior to the Hawley priority date is shown in the enclosed Press Release from PPL Therapeutics, Inc., entitled "World's First Cloned Double Knock-Out Pigs Lack Both Copies of Gene Involved in Hyperacute Rejection in Humans" and dated August, 2002.

These arguments are not persuasive because: A) as discussed in the previous office action mailed on 10/3/08 page 4, the cited reference by Hawley et al, (US 2006/0242722 A1) claims priority of the US Provisional Application No. 60/403,405, August 14, 2002 which is before the claiming priority of August 21, 2002 of the instant application. The US Provisional Application No. 60/403,405, August 14, 2002 does not need to provide reduction to practice of the invention. Hawley et al, teach the production of piglets using cell clones lacking wild-type α1,3-Galactosyltransferase (GGTA1), wherein the expression of the α1,3-Galactosyltransferase activity in the GGTA1 null animals was negative, organs and cells from said null pigs. Second, the claimed invention is not limited to the production of homozygous α(1,3) galactosyltransferase pigs by nuclear transfer by knocking out one allele of the α(1,3) galactosyltransferase gene first by **conventional targeted homologous recombination-**

mediated disruption, but relying on selection of **a natural mutation on the second allele** of the porcine α(1,3) galactosyltransferase gene, in order to produce the claimed pigs. The invention as claimed reads on any α1, 3-Galactosyltransferase null pig via any method of creating said pig, therefore the production of piglets by Hawley using cell clones lacking wild-type α1, 3-Galactosyltransferase, wherein the expression of the α1, 3-Galactosyltransferase activity in the α1, 3-Galactosyltransferase null animals was negative, organs and cells from said null pigs anticipates the claimed invention (emphasis added). B) The Examiner is unable to find evidence showing that the pigs of Hawley were born after the pigs of the instant invention by examining The New Scientist article provided by the Applicants. Thus, said reference fails to antedate the Hawley reference. The evidence submitted is insufficient to establish that both conception and reduction to practice of the present invention was completed prior to Hawley's provisional filing date.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims **1-18, 44-46, 49-59, 61, 63-65 remain** rejected under 35 U.S.C. 103(a) as being unpatentable over **Lai et al,** (Science, 295: 1089-1092, February 2002) in view of **Straham et al,** (Frontiers in Bioscience, 1, e34-41, 1996).

Applicants argue that do not dispute that the art recognized a need for alpha-negative swine to produce useful tissues for xenotransplantation. What Applicants dispute is that there

was any expectation in the art that such animals would be viable. The Examiner has asserted that any such skepticism was overcome when it was shown aGT-negative mice were viable. However, as discussed below, at the time of filing there were well recognized differences in alpha Gal epitope expression between mice and pigs, based on which one of ordinary skill in the art would have lacked any expectation that results obtained in mice could be applied to pigs. Applicants submit that none of the cited references overcome the documented skepticism in the art that an aGT- negative pig would be viable and thus none of the references, alone or in combination, render the present invention obvious.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Lai teaches the production of a-1,3-galactosyltransferase heterozygotes and also teaches the next step will be to create a-1,3-galactosyltransferase–null (homozygous knockout) pigs, either by breeding to a heterozygous male produced by nuclear transfer or by sequential nuclear transfer modification of cell lines produced from the four female pigs produced by Lai (p 1092, 1st column, last paragraph). Because a-1,3-alactosyltransferase–null mice have already been produced, it is not anticipated that this genetic modification will be lethal in the null animals. Lai suggests that a-1,3-galactosyltransferase–null pigs will not only eliminate hyperacute rejection but also ameliorate later rejection processes, and (in conjunction with clinically relevant immunosuppressive therapy) will permit long-term survival of transplanted porcine organs (p 1092, 1st column, last paragraph). At a minimum, the availability of

galactosyltransferase-null pigs will allow a clearer evaluation of approaches currently in development aimed at overcoming potential delayed and chronic rejection mechanisms in porcine xenotransplantation (p 1092, 1st column, last paragraph). Strahan et al teach the α(1,3) galactosyltransferase epitope is the major target for human anti-pig natural antibodies leading to the events that precipitate the hyperacute rejection; teaches attempts are being made to produce transgenic pigs with reduced levels of expression of the α(1,3) galactosyltransferase epitope and as such, Strahan et al provide sufficient motivation for one of ordinary skill in the art to breed the heterozygous α(1,3) galactosyltransferase pigs produced by Lai in order to obtain homozygous pigs with no expression of the α(1,3) galactosyltransferase.

Applicants argue Tanemura and **Galili** reference teach that pig organs express between 10 and 500 times the a-Gal levels of mice organs. Tanemura and Galili note that, the observed extensive expression of a-gal epitopes in pig organs raises the possibility that this epitope may have certain biological roles in pigs. If this assumption is correct, then pigs may not be able to develop in the absence of a-gal epitopes. Similarly, **Galili** (Galili, U. (2001) Biochimie 83:557-563) notes that the abundant expression of a-Gal in pigs throws doubt onto whether a homozygous aGT-negative animal would survive. As the Applicants have noted previously, the production of viable pigs lacking a-Gal would have been considered merely a wished for result prior to the present invention because the lack of a-Gal, normally present on the surface of all pig cells, would have been expected to be lethal. As noted in Galili, "Even if one succeeds in generating heterozygote pigs in which one of the two al,3GT genes is disrupted, it is not clear at present whether a homozygous pig with two disrupted al,3GT genes can develop." (see page 560). In addition, Galili notes that the difference between mice and pigs, and indeed between pigs and all other animals', casts doubt as to whether viability of any other low-Gal animal could

be applied to pigs. Galili states, That the a-gal epitope is not an essential epitope in most mammals is implied from the 'natural' knock-out of this gene in primate evolution and from the recent successful knock-out in mice. We have recently found, however, that the expression of a-gal epitopes in pig kidney is 500- to 1000-fold higher than in mouse kidney. Also in other organs such as heart, lung, or liver, expression of a- gal epitopes is many fold higher in the pig than in the mouse. This raises the concern that the abundantly expressed a-gal epitope may have some biological roles in pig development, such as in cell-cell interaction. If this assumption is correct, pigs may not develop in the absence of this epitope. (emphasis added). These references support that skilled artisans lacked an expectation that any aGT-negative pig would be viable, even after the development of aGT-null mice. We have also previously presented numerous additional references that support the high level of skepticism surrounding the production of viable pigs lacking a-Gal expression that existed prior to the Applicants' invention. For example, **Ayares et** al. (2001) Graft 4:80-85 note "[since] Gal epitope expression in pig organs is up to 500-fold higher than in mouse organs, there is the possibility that aGT activity is more crucial to the pig"; **Sharma et al. (2003)** Transplantation 75:430-436 note "it is possible that GT(-/-) pigs may not be viable because the GT gene is essential for embryonic development"; and **Porter & Dallman (1997**) Transplantation 64:1227-1235 note "[a]lthough [aGT-negative mice] develop and remain fairly normal, the possibility exists that deletion of this enzyme could have more severe consequences in other animals".

These arguments are not persuasive because while all the above references raise the concern that the abundantly expressed a-gal epitope may have some biological roles in pig development, such as in cell-cell interaction however, Lai teaches a-1,3-alactosyltransferase–null mice have already been produced, and it is not anticipated that this genetic modification will be lethal in the null animals. Lai suggests that a-1,3-galactosyltransferase–null pigs will not only

eliminate hyperacute rejection (p 1092, 1st column, last paragraph). Strahan et al teach the α(1,3) galactosyltransferase epitope is the major target for human anti-pig natural antibodies leading to the events that precipitate the hyperacute rejection; teaches attempts are being made to produce transgenic pigs with reduced levels of expression of the α(1,3) galactosyltransferase epitope and as such, Strahan et al provide sufficient motivation for one of ordinary skill in the art to breed the heterozygous α(1,3) galactosyltransferase pigs produced by Lai in order to obtain homozygous pigs with no expression of the α(1,3) galactosyltransferase.

Applicants argue for example, **Denning** and colleagues attempted to produce aGT sheep and were unable to achieve any live births (Denning et al. (2001) Nature Biotech 19:559-562). Without an animal surviving for sufficient time to grow useful organs, no organs or tissues could be produced that could be used for xenotransplantation.

These arguments are not pertinent to the instant rejection because the combining teachings of Lai/ Strahan suggest the survival of homozygous pigs with no expression of the α(1,3) galactosyltransferase, therefore provide teachings for animal surviving for sufficient time to grow useful organs that could be used for xenotransplantation.

Claims 19-21 remain to appear to be free of the prior art of record but are depended from rejected claims.

Conclusion

No claim is allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the

application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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/Anne-Marie Falk/
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